APPENDIX A. SUMMARY OF EXTERNAL PEER COMMENTS AND DISPOSITION

This appendix will be added after the external peer review.

APPENDIX B. INHALATION CANCER ASSESSMENT CALCULATIONS

In the 1998 NTP inhalation study, groups of male and female B6C3F$_1$ mice were exposed to chloroprene concentrations of 0, 12.8, 32, or 80 ppm chloroprene for 6 hours/day, 5 days/week, for up to 105 weeks. Statistically significant increases in tumor incidence were observed at multiple sites: the circulatory system (hemangiomas, hemangiosarcomas), lung (bronchiolar/alveolar adenomas and carcinomas), forestomach, harderian gland, kidney (males), skin (females), liver (females), and mammary gland (females). These incidences are provided in Table B-1. Note that statistically significant increases in hemangioma or hemangiosarcoma (male), lung cancer incidence (male and female), liver (female), and skin (female) were observed at chloroprene exposure levels down to 12.8 ppm, the lowest level tested (NTP, 1998). Furthermore, survival for all chloroprene-exposed female mice and for male mice in the two higher exposed groups was statistically significantly lower than for the corresponding control mice.

Dose-response analysis for carcinogenicity can be an iterative process, especially in the case of multiple tumor sites, as here. Quantal dose-response analysis of the more significant tumor sites was carried out as a baseline, and for comparison with other chemicals assessed for carcinogenicity, mainly through quantal analysis. Since decreased survival was significantly associated with chloroprene exposure, however, time-to-tumor analysis is an essential component of the dose-response assessment of its carcinogenic potential. Both phases are detailed below.

Exposure Conversions to Human Equivalent Concentrations

For both approaches to dose-response analysis, the exposure concentrations, presented in ppm units in the report, were weighted by time (5 days exposure × 1 week/7 days, 6 hours exposure × 1 day/24 hours) to obtain equivalent continuous exposure, or duration-adjusted, concentrations (see Table B-2). There were no relevant data characterizing internal doses of reactive chloroprene metabolites, or for chloroprene absorption. Under EPA's proposed new cancer risk assessment guidelines (U.S. EPA, 1996), the default adjustment to convert animal exposure concentrations to human equivalent concentrations (HECs) depends upon the critical target (U.S. EPA, 1994).

The HEC for thoracic effects is derived by multiplying the duration-adjusted concentrations by an interspecies dosimetric adjustment for gas:respiratory effects in the thoracic region of the lung, according to the following calculation (U.S. EPA, 1994b):

$$RGDR(TH) = (MV_a/S_a)/(MV_h/S_h)$$

where

RGDR(TH) = regional gas dose ratio for the thoracic (tracheobronchial and pulmonary) area of the lung

MV_a = animal minute volume (mouse = 0.061 m^3/day)

MV_h = human minute volume (20 m^3/day)
S_a = surface area of the thoracic region of the animal lung (mouse = 503.5 cm^2)
S_h = surface area of the thoracic region of the human lung (543,200 cm^2).

Using these default values, the RGDR(TH) = (0.061/503.5)/(20/543200) = 3.3.

For extra-respiratory effects, no adjustment of the duration-adjusted concentrations was made, since the air:blood partition coefficients for mice and humans for chloroprene are unknown, and dosimetry defaults to equivalence of inhalation concentrations across species (U.S. EPA, 1994). By analogy with butadiene (U.S. EPA, 1998), it is possible that the respiratory effects could have resulted from systemic exposure to chloroprene and its derivatives, in which case the HECs used for the extra-respiratory effects would also apply for the lung tumor analysis. The HECs for both direct respiratory effects and systemic effects are listed in Table B-2.

Quantal Dose-Response Analysis

When EPA estimates cancer risks for humans from rodent bioassay data, the risk estimates are most often calculated from the incidence of rodents of the most sensitive species, strain, and sex bearing tumors at any of the sites displaying treatment-attributable increases. For chloroprene, mice were the more sensitive species, with both sexes showing similar dose-response patterns for several tumor types (hemangiomas or hemangiosarcomas, alveolar/ bronchiolar adenomas and carcinomas), with female mice having additional tumor types.

When survival is not significantly affected by exposure, EPA uses the linearized multistage (LMS) model to estimate a 95% upper confidence limit (UCL) incremental lifetime unit cancer risk (extra risk) for humans. The multistage model has the form:

$$P(d) = 1 - \exp [-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)],$$

where P(d) represents the lifetime risk (probability) of cancer at dose (i.e., human equivalent exposure concentration, in this case) d, and parameters $q_i \geq 0$, for i=0, 1, ..., k. Note that modest impacts on survival can be addressed by omitting the animals in each treatment group who died before the first occurrence of the tumors being analyzed. Extra risk over the background tumor rate is defined as

$$[P(d) - P(0)] / [1 - P(0)].$$

Point estimates of the dose coefficients (q_is), and consequently the extra risk function, at any dose d are calculated by maximizing the likelihood function with respect to the tumor incidence data. The incremental lifetime unit cancer risk for humans (q_1^*) is defined as the 95% UCL on the parameter q_1, which is the linear dose coefficient, for extra risk. This 95% UCL represents a plausible upper bound for the true risk. The 95% UCL was calculated using the computer program GLOBAL86 (Van Landingham and Howe, 1990). Both the model and the curve-fitting methodology used are described in detail by Anderson et al. (1983).

The strongest site-specific dose-response patterns were judged by inspection to be the lung tumor incidence for female mice (Table B-2), and the hemangiosarcoma and hemangioma incidence for male mice (Table B-3). GLOBAL86 inputs, using the HECs described above and survival-adjusted incidence rates, are also listed in these tables. The q_1* for humans, for continuous lifetime inhalation exposure to chloroprene, calculated from the female lung tumors is 0.31/ppm (8.6×10^{-5} per ：g/m^3) if the mode of action involves systemic exposure, or 0.093/ppm (2.6×10^{-5} per ：g/m^3) if chloroprene acts before entering the circulatory system (Table B-2). Table B-3 shows the q_1* for humans calculated from the male mouse circulatory system tumors is 0.12 per ppm (3.4×10^{-5} per ：g/m^3). These risk estimates are fairly similar, with the q_1* based on male mouse circulatory tumors differing from each of the female mouse lung tumor unit risks by about a factor of two, but closer to the direct-mode lung tumor unit risk. Note that if chloroprene's mode of action for the female lung tumors were a combination of direct and systemic exposure, the unit risk would more likely be intermediate between these two estimates, and still quite similar to the male mouse circulatory system tumor unit risk. Based on this single-site per sex analysis, neither species is clearly more sensitive than the other.

Under EPA's proposed new cancer risk assessment guidelines (U.S. EPA, 1996), unit cancer risk estimates for genotoxic chemicals would be derived by straight linear extrapolation to 0 (no exposure) from the LED_{10} (estimated 95% lower confidence limit the dose corresponding to a 10% extra cancer risk). Using the LEC_{10} generated for the LMS model by GLOBAL86 for these tumors yields unit cancer risks very similar to the q_1^*s already calculated.

So many sites demonstrated significant tumor increases attributable to chloroprene that single site evaluations may underestimate the carcinogenic potential of chloroprene, especially in the case of the female mice. When all of these tumor sites are combined, however, overall background incidence levels for these sites obscure the effects of chloroprene. This 'flattening' of the dose-response relationship results from the inability of the LMS model to allow for (primarily) single tumors in control animals and multiple tumors in treated animals. One approach to assessing the risk of multiple tumor types is to derive risk estimates from responsive sites with low background tumor incidence in female mice: hemangiomas or hemangiosarcomas, mammary gland adenocanthomas or carcinomas, liver carcinomas, and skin and mesentery sarcomas. Under the direct mode of action hypothesis, lung tumors were omitted, since the higher exposure level could not be accommodated by the LMS procedure. Consequently, this combined estimate could still underestimate the overall carcinogenic potential of chloroprene. As in the previous GLOBAL86 analyses, deaths occurring before the earliest occurrence of any of these tumors were omitted from the calculations. In addition, the lung tumors were included in a second analysis, assuming a systemic mode of action is appropriate for all of the tumor types considered. The GLOBAL86 inputs for fitting both sets of incidences are given in Table B-4.

The results of analyzing these combined incidences are provided in Table B-4. The q_1* for humans calculated from the combined, less common extra-respiratory female mouse tumors is 0.23 per ppm (6.4×10^{-5} per ：g/m^3), for continuous lifetime inhalation exposure to chloroprene. This is slightly lower, but similar to the earlier systemic-mode lung tumor-based unit risk (0.31/ppm, or 8.6×10^{-5} per ：g/m^3), and about twofold higher than the unit risk for lung

tumors alone. The unit risk resulting from modeling the combined incidences, and also assuming a systemic mode of action for lung tumors, is 0.40/ppm, a 30% increase over the corresponding unit risk for lung tumors alone.

A similar analysis was carried out for less common tumors in male mice: circulatory system hemangiomas and hemangiosarcomas, forestomach adenomas and carcinomas, harderian gland adenomas and carcinomas, and renal tubule adenomas. Lung tumors were specifically omitted because of their higher background rate in the control animals (13/50=26%, Table B-1). Table B-5 summarizes the inputs and results. The combined unit risk for these tumors was 0.17/ppm (4.6×10^{-5} per $\mu g/m^3$), a 40% increase over the unit risk based on circulatory system tumors alone. The female mouse unit risks accounting for multiple tumors are clearly higher.

The unit cancer risk estimates (95% UCL) derived above are intended to be plausible upper limits on the risk of developing any chloroprene-attributable tumor over a full (70-year) lifetime. They also provide points of comparison with assessments of other chemicals with similar dose-response patterns. However, as noted above, using the quantal incidence data for total tumor-bearing mice in each exposure group does not fully characterize the cancer potency reflected by the mouse bioassay results. First, the methodology does not take into account the fact that many of the mice in the higher exposure groups had tumors at multiple significant sites, only that at least one tumor was observed. Second, the methodology ignores the fact that survival was significantly decreased in female mice exposed to 12.8 ppm or more chloroprene as a result of chloroprene-attributable tumors. The omission of deaths occurring before the first relevant tumor is only a crude adjustment, and does not allow for the possible accelerated occurrence of tumors with increasing exposure. Time-to-tumor analyses conducted for specific tumor sites are presented below and can be used to evaluate the time component of the cancer risk.

Time-to-Tumor Dose-Response Analysis

The mouse inhalation bioassay results demonstrate different dose-response relationships for different tumor sites. To assess the characteristics of the dose-response relationships for different tumor sites, time-to-tumor analyses were performed to adjust for competing mortality from cancer at other sites. These time-to-tumor analyses were conducted from the individual mice data, for sites demonstrating an increased cancer incidence, as noted in the NTP report. Benign and malignant tumors were combined for sites where appropriate. Thus time-to-tumor analyses were performed for lung alveolar/ bronchiolar adenomas or carcinomas; hemangiomas and hemangiosarcomas; harderian gland adenomas; forestomach squamous cell papillomas or carcinomas; and hepatocellular carcinomas, skin sarcomas and mammary gland carcinomas (females). Kidney renal tubule adenomas (males) were not analyzed because the additional mice with tumors detected in the extended evaluation were not individually identified in the NTP report. Tumor types were not combined across sites prior to modeling, because this would interfere with elucidating the different time courses of each tumor type.

The general model used for the time-to-tumor (or time-to-response) analyses was the multistage Weibull model, which has the form

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z]$$

where P(d,t) represents the probability of a tumor (or other response) by age t (in bioassay weeks) for dose d (i.e., human equivalent exposure), and parameters $z \geq 1$, $t_0 \geq 0$, and $q_i \geq 0$ for i=0, 1, ..., k, where k = the number of dose groups - 1. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death (see below). The analyses were conducted using the computer software TOX_RISK version 3.5 (Crump et al., ICF Kaiser International, Ruston, LA), which is based on Weibull models taken from Krewski et al. (1983). Parameters are estimated using the method of maximum likelihood.

Tumor types were categorized by tumor context as either fatal or incidental tumors, in order to adjust appropriately for competing risks. Incidental tumors are those tumors thought not to have caused the death of an animal, while fatal tumors are thought to have resulted in animal death. Hemangiomas and hemangiosarcomas were treated as fatal tumors, unless observed at the terminal sacrifice, in which case they were considered incidental. Furthermore, these tumors were considered rapidly fatal, and t_0 was set equal to 0, as there were insufficient data to reliably estimate t_0 in any event. Tumors at all other sites were treated as incidental. This is consistent with the determination made by EPA for 1,3-butadiene (U.S. EPA 1998). The work of Portier et al. (1986) analyzing tumor types in NTP historical controls lends support to these tumor context assumptions.

Specific n-stage Weibull models were selected for the individual tumor types for each sex based on the values of the log-likelihoods according to the strategy used by EPA (U.S., 1998). If twice the difference in log-likelihoods was less than a chi-square with degrees of freedom equal to the difference in the number of stages included in the models being compared, then the models were considered comparable and the most parsimonious model (i.e., the lowest-stage model) was selected. Parameter estimates for the time-to-tumor analyses for each tumor type are presented in Table B-6. For all tumor types except the hemangiosarcomas and hemangiomas in female mice, the one-stage Weibull was the preferred model. The hemangiosarcomas and hemangiomas in female mice were best described by the two-stage Weibull model.

Human unit cancer risk (or potency) estimate results (extra risk) are presented in Table B-7. Lung tumors in female mice convey the greatest amount of extrapolated risk to humans, whether or not the mode of action is assumed to be direct, at 0.21/ppm (5.9×10^{-5} per $\mu g/m^3$)) or systemic, at 0.69/ppm (1.9×10^{-4} per $\mu g/m^3$). Hemangiomas/hemangiosarcomas and lung tumors in male mice also convey a similar amount of extrapolated risk to humans: hemangioma/hemangiosarcoma $q_1^* = 0.23$/ppm (6.5×10^{-5} per $\mu g/m^{3)}$ chloroprene exposure; lung tumor $q_1^* = 0.15$/ppm (4.1×10^{-5} per $\mu g/m^3$) by the direct-mode, or 0.49/ppm (1.4×10^{-4} per $\mu g/m^3$) by the systemic mode. Note that the time-to-tumor unit risks for male hemangiomas and hemangiosarcomas, and for female lung tumors, are about twofold higher that their quantal analysis counterparts.

Although the time-to-tumor modeling does help account for decreased survival times in the mice, considering the tumor sites individually still does not convey the total amount of risk potentially arising from the sensitivity of multiple sites. To get some indication of the total unit risk from multiple tumor sites, assuming the multiple sites are mechanistically independent, the MLEs of the unit potency from the Weibull time-to-tumor models were summed across tumor sites and estimates of the 95% upper bound on the summed unit potency were calculated. The TOX_RISK software provides MLEs and 95% UCLs for human risk at various exposure levels, allowing for the calculation of unit potency estimates at those exposure levels.

When the MLEs of unit potency from the female mouse data (Table B-7) were summed across the mouse tumor sites, the MLE of the total unit risk was 0.35/ppm (direct mode of action assumed for the lung tumors) or 0.71/ppm (systemic mode of action for the lung tumors), assuming continuous lifetime chloroprene exposure. Summing the q_1*s across the female mouse tumor sites yielded 0.63/ppm and 1.1/ppm, respectively; this approach is statistically incorrect, however, resulting in overestimates of the upper bounds. A statistically correct 95% upper bound for the total potency was calculated by assuming a normal distribution for the risk estimates, deriving the variance of the risk estimate for each tumor site from its 95% UCL according to the formula

$$95\%\ \text{UCL} = \text{MLE} + 1.645\sigma,$$

where the standard deviation σ is the square root of the variance. The variances were summed across tumor sites to obtain the variance of the sum of the MLEs. The 95% UCL on the sum of the MLEs was calculated from the variance of the sum using the same formula. The resulting 95% UCLs on the unit potency for the total unit risk were 0.48/ppm (direct-mode) and 0.92/ppm (systemic-mode). The results of these summation analyses are summarized in Table B-8.

These unit potencies for the female mouse data were also summed using a Monte Carlo analysis and the software Crystal Ball version 4.0 (Decisioneering, Denver, CO). Normal distributions were assumed for the unit potency for each tumor site, with the mean equal to the MLE and σ as calculated from the above formula. A distribution around the sum of the MLEs was then generated by simulating the sum of unit potencies picked from the distributions for each tumor site (according to probabilities determined by those distributions) 10,000 times. The mean for the sum and the 95th percentile on the distribution were the same as the sum of MLEs and 95% UCL calculated above, as they should be. However, a sensitivity analysis (based on contribution to variance) for the sum incorporating the direct-mode lung tumor unit risk, revealed that variability associated with the circulatory system tumors unit potency estimate was contributing about 50% of the variance in the sum, while the unit risk contributed essentially nothing to the overall sum. Excluding the circulatory system tumors yielded the same MLE of total risk, 0.35/ppm, while 95% UCL decreased slightly to 0.44/ppm. The lung tumors, which contributed the most to that sum, contributed about 42% of the variance, followed by the liver with 35%. For the overall sum incorporating the systemic-mode lung tumor unit risk, the lung unit risk contributed the most to the sum and the variance, at 72%. The other sites had little

impact on the MLE of risk and less on the upper bound. The results of these summation analyses are summarized in Table B-8.

The same analyses were performed summing the estimates of unit potency derived from the male mouse data for the different tumor sites (from Table B-7). The resulting MLE for the total unit risk was 0.36/ppm lifetime chloroprene exposure, with a 95% UCL of 0.51/ppm., incorporating a direct-mode of action for lung tumors. Circulatory system tumors contributed about 41% to the variance of this sum, and about half of the sum. Consequently, the unit risk for circulatory system tumors was retained in the sum. Alternatively, for a systemic mode of action for lung tumors, the MLE for the total unit risk was 0.61/ppm lifetime chloroprene exposure, with a 95% UCL of 0.76/ppm. As with the parallel analysis for female mice, this site was the single most significant contributor to the total unit risk, assuming a systemic mode of action. The results of these summation analyses are also summarized in Table B-8.

Discussion

Based on the analyses discussed above, the best estimate for an upper bound on human extra cancer risk from continuous lifetime exposure to chloroprene, derived from animal data, is about 0.48/ppm (1.3×10^{-4} per $\mu g/m^3$), or 0.92/ppm (2.6×10^{-4} per $\mu g/m^3$) depending upon whether the mode of action for generating lung tumors involves direct or systemic exposure to chloroprene. These estimates reflect the time-to-tumor response as well as the exposure-response relationships for the multiple tumor sites in the most sensitive species.

Note that Melnick et al. (1999) have reported the EC10 for chloroprene to be 0.3 ppm, based on a analysis of female mouse lung tumors, adjusted for survival. The corresponding EC10 in this analysis is reported in Table B-2 at 0.4 ppm, LEC10 at 0.3 ppm. When time-to-tumor was incorporated in the analysis, the EC10 for lung tumors (systemic-mode) decreased to 0.2 ppm (0.7 mg/m^3, Table B-7). On a site-specific basis, this analysis is in general agreement with that of Melnick et al. (1999).

The greatest source of uncertainty in these estimates is from the interspecies extrapolation of risk from the mouse to humans. The two rodent species for which bioassay data were available—the mouse and the rat—varied significantly in their carcinogenic responses to chloroprene, in terms of both site specificity and magnitude of response. The mouse was the more sensitive species to the carcinogenic effects of chloroprene exposure and, hence, the more conservative (i.e., public health protective) for the extrapolation of risk to humans. Note that EPA's risk assessment for 1,3-butadiene included some human data which resulted in unit risk of 0.03/ppm, while the tumor-specific unit risks based on animal data were very similar to those calculated for chloroprene in this analysis (U.S. EPA, 1998).

In addition to uncertainties pertaining to the relevance of the rodent models to human risk, there is uncertainty in quantitatively scaling the animal risks to humans. Ideally, a PBPK model for the internal dose(s) of the reactive metabolite(s) would decrease some of the quantitative uncertainty in interspecies extrapolation; however, none is available.

Another major source of uncertainty in the unit potency estimates is the extrapolation of high-dose risks observed in the mouse bioassay to lower doses that would be of concern from human environmental exposures. A multistage Weibull time-to-tumor model was the preferred model because it can take into account the differences in mortality between the exposure groups in the mouse bioassay; however, it is unknown how well this model is predicting the low-dose extrapolated risks for chloroprene.

References

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Table B-1. Tumor incidence in female and male mice exposed to chloroprene via inhalation (NTP, 1998)

Sex	Tissue	Administered Chloroprene Concentration			
		Control	12.8 ppm	32 ppm	80 ppm
Females	Circulatory system: hemangioma or hemangiosarcoma	4/50	6/49	18/50	8/50
	Lung: alveolar/bronchiolar adenoma, carcinoma	4/50	28/49	34/50	42/50
	Liver: hepatocellular carcinoma	4/50	11/49	14/50	19/50
	Forestomach: squamous cell papilloma or carcinoma	1/50	0/49	0/50	3/50
	Harderian gland: adenoma	1/50	3/49	3/50	8/50
	Mammary gland: carcinoma and adenocanthoma	3/50	5/49	10/50	14/50
	Skin: sarcoma	0/50	11/49	11/50	18/50
	Mesentery: sarcoma	0/50	4/49	8/50	3/50
Males	Circulatory system: hemangioma or hemangiosarcoma (excluding liver)	1/50	12/50	18/50	17/50
	Lung: alveolar/bronchiolar adenoma, carcinoma	13/50	28/50	36/50	43/50
	Forestomach: squamous cell papilloma	1/50	0/50	2/50	4/50
	Harderian gland: adenoma, carcinoma	2/50	5/49	10/50	12/50
	Kidney: renal tube adenoma, standard and extended evaluations combined	0/50	2/49	3/50	9/50

Table B-2. Summary of quantal analysis of female mice lung tumor incidence, adjusted for survival

Dose-response data	Administered Concentration (ppm)	Adjusted incidence[a]:	Human Equivalent Concentration (ppm)	
			for Systemic Effects[b]	for Direct Respiratory Effects[c]
	0 12.8 32 80	4/49 28/47 34/49 42/48	0 2.3 5.7 14.3	0 7.5 18.9 47.1
Results[d]	MLEs of dose coefficients[e]:		q_0 =0.1008 q_1 =0.2380/ppm	q_0 =0.1008 q_1 =0.0722/ppm
	p-value for chi-square goodness of fit		0.015	0.015
	q_1* (95% UCL on extra risk, at 1 ∶g/m^3)		3.1 x 10^{-1}/ppm, or 8.6 x 10^{-5}/(∶g/m^3)[d]	9.3 x 10^{-2}/ppm, or 2.6 x 10^{-5}/(∶g/m^3)
	MLE of extra risk at 1 ∶g/m^3		6.6 x 10^{-5}/(∶g/m^3)	2.0 x 10^{-5}/(∶g/m^3)
	EC_{10}		0.4 ppm, or 1.6 mg/m^3	1.5 ppm, or 5.3 mg/m^3
	LEC_{10} (lower 95% bound on exposure at 10% extra risk)		0.3 ppm, or 1.2 mg/m^3	1.1 ppm, or 4.1 mg/m^3
	$0.1/LEC_{10}$ (slope from POD to background)		2.8 x 10^{-1}/ppm, or 8.0 x 10^{-5}/(∶g/m^3)	8.8 x 10^{-2}/ppm , or 2.4 x 10^{-5}/(∶g/m^3)

[a] Deaths occurring before the first observed tumor, Week 47 for lung tumors, were omitted.
[b] Adjusted to continuous exposure by multiplying by 6/24 (hours) x 5/7 (days) = 0.178.
[c] Multiplied continuous exposure by RGDR(TH) = 3.3.
[d] Results of fitting the 3 lower dose groups, using GLOBAL86; the model fit was poor when the high dose was included (p=0.008).
[e] $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)]$, where d is ppm chloroprene.
[f] 1 ppm chloroprene = 3.6 mg/m^3.

Table B-3. Summary of quantal analysis of male mice hemangioma and hemangiosarcoma incidence, adjusted for survival

Dose-response data	Administered concentration (ppm)	Adjusted incidence[a]	Human Equivalent Concentration (ppm)
	0	1/50	0
	12.8	12/49	2.3
	32	18/48	5.7
	80	17/48	14.3
Results[b]	MLEs of dose coefficients[c]:		q_0 =0.0230 q_1 =0.0885/ppm
	p-value for chi-square goodness of fit		0.20
	q_1* (95% UCL on extra risk, at 1 ∶g/m^3)		1.2 x 10^{-1}/ppm, or 3.4 x 10^{-5}/(∶g/m^3)[d]
	MLE of extra risk at 1 ∶g/m^3		2.5 x 10^{-5}/(∶g/m^3)
	EC_{10}		4.3 mg/m^3
	LEC_{10} (lower 95% bound on exposure at 10% extra risk)		3.1 mg/m^3
	$0.1/LEC_{10}$ (slope from POD to background)		1.2 x 10^{-1}/ppm , or 3.2 x 10^{-5}/(∶g/m^3)

[a] Deaths occurring before the first observed tumor, Week 65, were omitted.
[b] Results of fitting the 3 lower dose groups; the model fit was poor when the high dose was included (p=0.004).
[c] $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)]$, where d is ppm chloroprene.
[d] 1 ppm chloroprene = 3.6 mg/m^3.

Table B-4. Summary of quantal analysis of female mice, multiple tumor incidence[a] adjusted for survival

Dose-response data	Administered concentration (ppm)	HEC (ppm)	Survival adjusted incidence[a]:	
			Extra-respiratory tumors	and lung tumors
	0 12.8 32 80	0 2.3 5.7 14.3	9/49 29/50 37/50 44/49	14/49 37/50 43/50 48/49
Results	MLEs of dose coefficients :		q_0 =0.2553[b] q_1 =0.1779/ppm	q_0 =0.3780 q_1 =0.3035/ppm
	p-value for chi-square goodness of fit		0.09	0.17
	q_1* (95% UCL on extra risk, at 1 μg/m^3)		2.3 x 10^{-1}/ppm, or 6.4 x 10^{-5}/(μg/m^3)[c]	4.0 x 10^{-1}/ppm, or 1.1 x 10^{-4}/(μg/m^3)
	MLE of extra risk at 1 ppb		4.9 x 10^{-5}/(μg/m^3)	8.4 x 10^{-5}/(μg/m^3)
	EC_{10}		2.1 mg/m^3	1.2 mg/m^3
	LEC_{10} (lower 95% bound on exposure at 10% extra risk)		1.7 mg/m^3	1.0 mg/m^3
	$0.1/LEC_{10}$ (slope from POD to background)		2.2 x 10^{-1}/ppm, or 6.0 x 10^{-5}/(μg/m^3)	3.8 x 10^{-1}/ppm, or 1.0 x 10^{-1}/(μg/m^3)

[a] Extra-respiratory tumors: circulatory system hemangiomas and hemangiosarcomas, mammary adenocanthomas and carcinomas, liver carcinomas, and skin and mesentery sarcomas. Deaths occurring before Week 31, when the first hemangiosarcoma was observed, were omitted.

[b] $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)]$, where d is ppm chloroprene.

[c] 1 ppm chloroprene = 3.6 mg/m^3.

Table B-5. Summary of quantal analysis of male mice, extra-respiratory tumor incidence, adjusted for survival

Dose-response data	Administered concentration (ppm)	HEC (ppm)	Adjusted incidence[a]:
	0 12.8 32 80	0 2.3 5.7 14.3	3/50 16/49 25/48 25/48
Results[b]	MLEs of dose coefficients[c]:		q_0 =0.0656 q_1 =0.1255/ppm
	p-value for chi-square goodness of fit		0.30
	q_1* (95% UCL on extra risk, at 1 $\mu g/m^3$)		1.7×10^{-1}/ppm , or $4.6 \times 10^{-5}/(\mu g/m^3)$[d]
	MLE of extra risk at 1 $\mu g/m^3$		$3.5 \times 10^{-5}/(\mu g/m^3)$
	EC_{10}		3.0 mg/m^3
	LEC_{10} (lower 95% bound on exposure at 10% extra risk)		2.2 mg/m^3
	$0.1/LEC_{10}$ (slope from POD to background)		1.6×10^{-2}/ppm , or $4.5 \times 10^{-5}/(\mu g/m^3)$

[a] Circulatory system hemangiomas and hemangiosarcomas, forestomach adenomas and carcinomas, harderian gland adenomas and carcinomas, and renal tubule adenomas. Deaths occurring before Week 65, when the first hemangiosarcoma was observed, were omitted.

[b] Results of fitting the 3 lower dose groups; the model fit was poor when the high dose was included ($p<0.01$).

[c] $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)]$, where d is ppm chloroprene.

[d] 1 ppm chloroprene = 3.6 mg/m^3.

Table B-6. Parameter estimates for multistage Weibull time-to-tumor model based on female mouse tumor incidence

Tumor type		Model Parameter Estimates[a]			
		q_0	q_1	q_2	z
Female mice					
Circulatory system: hemangioma or hemangiosarcoma[b]		4.15×10^{-14}	0.0	1.66×10^{-14}	6.10
Lung: alveolar/bronchiolar adenoma, carcinoma	Direct-mode	2.46×10^{-9}	3.79×10^{-9}	-	3.77
	Systemic mode	2.63×10^{-9}	1.33×10^{-8}	-	3.75
Liver: hepatocellular carcinoma		1.09×10^{-8}	7.91×10^{-9}	-	3.48
Forestomach: squamous cell papilloma or carcinoma		2.15×10^{-9}	1.18×10^{-9}	-	3.33
Harderian gland: adenoma		8.94×10^{-9}	8.29×10^{-9}	-	3.18
Mammary gland: carcinoma		6.61×10^{-4}	2.67×10^{-4}	-	1.00
Skin: sarcoma		0.0	4.85×10^{-5}	-	1.54
Male mice					
Circulatory system: hemangioma or hemangiosarcoma		3.49×10^{-22}	5.64×10^{-22}	-	10.0
Lung: alveolar/bronchiolar adenoma, carcinoma	Direct-mode	4.01×10^{-8}	7.56×10^{-9}	-	3.46
	Systemic mode	4.01×10^{-8}	2.50×10^{-8}	-	3.46
Forestomach: squamous cell papilloma		3.06×10^{-6}	1.32×10^{-6}	-	1.79
Harderian gland: adenoma		3.28×10^{-13}	2.03×10^{-13}	-	5.57

[a] $P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z]$, where d is ppm chloroprene, t is weeks until death with tumor.
[b] High dose dropped due to poor fit

Table B-7. Human unit cancer risk estimates (extra risk, computed for risks of 10^{-6}) based on mouse tumor incidences, using multistage Weibull time-to-tumor model

Tumor Type		MLE		q_1*		EC_{10}, mg/m^3	LEC_{10}, mg/m^3	0.1/LEC_{10}	
		/ppm	/(:g/m^3)	/ppm	/(:g/m^3)			/ppm	/(:g/m^3)
Female mice									
Circulatory system		1.9×10^{-4}	5.2×10^{-8}	9.1×10^{-2}	2.5×10^{-5}	6.3	3.5	1.0×10^{-1}	2.8×10^{-5}
Lung: alveolar/bronchiolar adenoma, carcinoma	Direct-mode[a]	1.5×10^{-1}	4.3×10^{-5}	2.1×10^{-1}	5.9×10^{-5}	2.5	1.8	2.0×10^{-1}	5.6×10^{-5}
	Systemic-mode[a]	5.1×10^{-1}	1.4×10^{-4}	6.9×10^{-1}	1.9×10^{-4}	0.7	0.6	6.6×10^{-1}	1.8×10^{-4}
Liver: hepatocellular carcinoma		8.4×10^{-2}	2.3×10^{-5}	1.4×10^{-1}	3.8×10^{-5}	4.5	2.8	1.3×10^{-1}	3.6×10^{-5}
Forestomach: squamous cell papilloma or carcinoma		6.4×10^{-3}	1.8×10^{-6}	2.0×10^{-2}	5.6×10^{-5}	59.7	18.8	1.9×10^{-2}	5.3×10^{-6}
Harderian gland: adenoma		2.3×10^{-2}	6.3×10^{-6}	4.8×10^{-2}	1.3×10^{-5}	16.8	7.9	4.5×10^{-2}	1.3×10^{-5}
Mammary gland: adenocanthoma or carcinoma		2.8×10^{-2}	7.8×10^{-6}	4.3×10^{-2}	1.2×10^{-5}	13.5	8.9	4.0×10^{-2}	1.1×10^{-5}
Skin: sarcoma		6.3×10^{-2}	1.7×10^{-5}	9.2×10^{-2}	2.6×10^{-5}	6.0	4.1	8.8×10^{-2}	2.4×10^{-5}
Male mice									
Circulatory system		1.8×10^{-1}	5.1×10^{-5}	2.3×10^{-1}	6.5×10^{-5}	2.1	1.6	2.2×10^{-1}	6.2×10^{-6}
Lung: alveolar/bronchiolar adenoma, carcinoma	Direct-mode[a]	1.1×10^{-1}	3.1×10^{-5}	1.5×10^{-1}	4.1×10^{-5}	3.5	2.5	1.4×10^{-1}	3.9×10^{-5}
	Systemic-mode[a]	3.6×10^{-1}	1.0×10^{-4}	4.9×10^{-1}	1.4×10^{-4}	1.0	0.8	4.7×10^{-1}	1.3×10^{-4}
Forestomach: squamous cell papilloma		5.9×10^{-3}	1.6×10^{-6}	2.3×10^{-2}	6.3×10^{-6}	64.1	16.7	2.2×10^{-2}	6.0×10^{-6}
Harderian gland: adenoma		6.8×10^{-2}	1.9×10^{-5}	1.1×10^{-1}	3.0×10^{-5}	5.6	3.5	1.0×10^{-1}	2.9×10^{-5}

[a] See Table B-2 for human equivalent doses.

Table B-8. Unit potency estimates (extra risk) summed across tumor sites

Tumor set		Estimates of Extra Risk (calculated at 1 ppb)		
		Sum of MLEs of extra risk, /ppm	**Sum of q_1*s, /ppm**	**95% UCL on sum, /ppm**
Female mice	All (lung, direct-mode) [a]	0.35	0.63	0.48
	All (lung, direct-mode) except circulatory system tumors	0.35	0.54	0.44
	All (lung, systemic-mode)	0.71	1.12	0.92
Male mouse	All (lung, direct-mode[b]	0.36	0.51	0.44
	All (lung, systemic-mode)	0.61	0.85	0.76

[a] Circulatory system, lung, liver, forestomach, harderian gland, mammary gland, skin.
[b] Circulatory system, lung, forestomach, harderian gland